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RESEARCH ARTICLE

The effect of carnosine treatment on prooxidant–antioxidant balance in liver, heart and brain tissues of male aged rats

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Abstract Carnosine (β-alanyl-L-histidine) is a dipeptide with antioxidant properties. Oxidative damage by free radicals is one of the mechanisms underlying the aging process. This study was done to investigate the effects of carnosine treatment on lipid peroxidation and antioxidant status of liver, heart, brain in male young and aged rats. At the initiation of study, young and aged rats were 5 and 22 months old, respectively. Carnosine (250 mg/kg, daily, i.p.) was administered for 1 month to rats. At the end of this period, malondialdehyde (MDA) and diene conjugate (DC) and protein carbonyl (PC) levels, glutathione (GSH), vitamin E and vitamin C levels and Cu,Zn-superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and glutathione transferase (GST) activities were determined in tissues of carnosine-treated young and old rats. Liver and heart, but not brain MDA and DC levels increased significantly in aged rats as compared to young rats. Liver PC levels were also significantly elevated. Significant decreases in GSH and vitamin C levels and SOD activities were detected in liver of aged rats, but vitamin E levels and GSH-Px and GST activities remained unchanged. Non-enzymatic and enzymatic antioxidants did not change in heart and brain of aged rats. Carnosine treatment decreased high MDA, DC and PC levels and caused significant increases in vitamin E level and SOD activity in the liver of aged rats. There were no changes in non-enzymatic and enzymatic antioxidants in the heart and brain of carnosine-treated aged rats. In conclusion, carnosine treatment was found to be useful in the decrease of age-related oxidative stress in the liver.

Keywords Carnosine · Aging · Oxidative stress · Antioxidant system · Rat

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Introduction

One of the mechanisms underlying the aging process is proposed to be the oxidative damage caused by free radicals (Harman 2001). Several researchers have reported that oxidative stress parameters increased in various tissues like liver (Tian et al. 1998; Wolf et al. 2005; Wong et al. 2006; Parıldar-Karpuzoğlu et al. 2008), heart (Wolf et al. 2005; Wong et al. 2006; Parıldar et al. 2008) and brain (Tian et al. 1998; Siqueira et al. 2005; Wolf et al. 2005) with increasing age. In addition, there are also several reports in the literature concerning non-enzymatic and enzymatic antioxidants in liver (Tian et al. 1998; Jayakumar et al. 2007; Parıldar-Karpuzoğlu et al. 2008), heart (Jayakumar et al. 2007; Parıldar et al. 2008) and brain (Tian et al. 1998; Jayakumar et al. 2007; Parıldar-Karpuzoğlu et al. 2008) during aging.

Carnosine (β-alanyl-L-histidine) is a dipeptide which is especially found at relatively high concentrations in long-lived nonmitotic mammalian tissues (Hipkiss 2000; Aldini et al. 2005; Boldyrev 2005). It has several functions such as membrane protecting activity, pH buffering capacity and metal chelating ability (Hipkiss 2000; Aldini et al. 2005; Boldyrev 2005). Carnosine is also a potent scavenger of reactive oxygen species and aldehydes. It inhibits lipid peroxidation and protein oxidation and prevents advanced glycation product formation (Hipkiss 2000; Aldini et al. 2005; Boldyrev 2005). Therefore, it has been proposed that carnosine may be an effective agent to prevent oxidative stress-induced pathologies such as ischemia-reperfusion (Stvolinsky and Dobrota 2000; Dobrota et al. 2005; Fouad et al. 2007), thioacetamide- and alcohol- induced liver damage (Mehmetçik et al. 2008; Liu et al. 2008), atherosclerosis (Rashid et al. 2007), diabetic complications (Lee et al. 2005), aging (Hipkiss 2006) and Alzheimer's disease (Hipkiss 2007). Carnosine levels have been reported to decrease in some tissues of aged rats (Stuerenburg and Kunze 1999) and senescence accelerated mice (Boldyrev et al. 2001). Indeed, a correlation between intramuscular carnosine concentrations and maximal lifespan in mammals has been revealed (Hipkiss and Brownson 2000). In addition, carnosine administration was demonstrated to increase average lifespan of senescence accelerated mice (Gallant et al. 2000) and Drosophila melanogaster (Yuneva et al. 2002). Therefore, some investigators have reported that carnosine may have anti-aging actions (Hipkiss 2008).

However, there is no study in the literature investigating the in vivo effect of carnosine on prooxidant–antioxidant balance in several tissues of aged animals. We aimed to investigate the effect of carnosine treatment on prooxidant and antioxidant status in liver, heart and brain tissues of young and aged rats. For this reason, malondialdehyde (MDA) and diene conjugate (DC) and protein carbonyl (PC) levels as oxidative stress parameters, and glutathione (GSH), vitamin E and vitamin C levels and Cu,Zn-superoxide dismutase (Cu,Zn-SOD), glutathione peroxidase (GSH-Px) and glutathione transferase (GST) activities to reflect antioxidant status, were determined. These parameters were also measured in tissues of rats treated with carnosine.

Materials and methods

Animals and treatments

Young (5 months) and aged (22 months) male Wistar rats were obtained from Center for Experimental Medical Research Institute of Istanbul University. The animals were allowed free access to food and water and were kept in wire-bottomed stainless steel cages. The experimental procedure used in this study met the guidelines of the Animal Care and Use Committee of the University of Istanbul. Carnosine and other chemicals were purchased from Sigma–Aldrich (USA).

Young and aged rats were divided into two subgroups as untreated and carnosine-treated. Carnosine (250 mg/kg; i.p.) was given daily for 1 month. At the end of this period, rats were fasted overnight and liver, heart and brain tissues of rats were quickly removed and washed in 0.9% NaCl and kept at −70°C until they were analyzed.

Methods

Tissues were homogenized in ice-cold 0.15 M KCl (10%, w/v). Lipid peroxidation was assessed by two different methods in the tissue homogenates. First, the levels of MDA were measured by thiobarbituric acid test (Ohkawa et al. 1979). The breakdown product of 1,1,3,3-tetraethoxypropane was used as standard. Second, DC levels were determined in tissue lipid extracts at 233 nm spectrophotometrically and calculated using a molar extinction coefficient of $2.52 \times 10^4\ M^{-1}\ cm^{-1}$ (Buege and Aust 1978). PC levels were measured according to method described by Reznick and Packer (1994), based on spectrophotometric detection of the reaction of 2,4-dinitrophenylhydrazine with protein carbonyl groups to form protein hydrazones.

GSH levels were measured with 5,5-dithiobis-(2-nitrobenzoate) at 412 nm in tissue homogenates (Beutler et al. 1979). Vitamin E and vitamin C levels were measured in tissue homogenates by the method of Desai (1984) and Omaye et al. (1979), respectively. Cu,Zn-SOD, GSH-Px and GST activities were determined in postmitochondrial fraction of the tissues, which was separated by sequential centrifugation. In brief, tissue homogenates were centrifuged at 600*g* for 10 min at 4°C to remove crude fractions. Then,

supernatants were centrifuged at 10,000*g* for 20 min to obtain the postmitochondrial fraction. Cu,Zn-SOD activity was assayed by its ability to increase the effect of riboflavin-sensitized photooxidation of o-dianisidine (Mylorie et al. 1986). GSH-Px (Lawrence and Burk 1976) and GST (Habig and Jacoby 1981) activities were measured using cumene hydroperoxide and 1-chloro-2,4-dinitrobenzene as substrates, respectively. Protein levels were determined using bicinchoninic acid (Smith et al. 1985).

Statistical analysis

The results were expressed as mean ± SD. Experimental groups were compared using Kruskal–Wallis variance analysis test. Where significant effects were found, post-hoc analysis using Mann–Whitney U test was performed, and $P < 0.05$ was considered to be statistically significant.

Results

The results are shown in Figs. 1, 2 and 3. According to this; MDA, DC and PC levels in the liver and MDA and DC levels in the heart increased significantly, but there were no changes in these values in brain of aged rats as compared to young ones (Fig. 1). Significant decreases in GSH and vitamin C levels were detected in liver of aged rats. Liver vitamin E levels increased in aged rats, but this increase was not significant (Fig. 2). Liver SOD activity decreased, but GSH-Px and GST activities remained unchanged in old rats (Fig. 3). However, non-enzymatic and enzymatic antioxidants did not change in heart and brain of aged rats (Figs. 2, 3).

No significant change in oxidative stress parameters was detected in liver, heart and brain of young rats following carnosine treatment. Carnosine treatment decreased high MDA, DC and PC levels in liver, but this treatment did not alter MDA and DC levels in the heart of aged rats (Fig. 1). Carnosine caused increases in liver GSH levels (13.5%), but this increase was not significant. On the other hand, significant increases were observed in vitamin E level and SOD activity in the liver of aged rats (Figs. 2, 3). Non-enzymatic and enzymatic antioxidants were found to be unchanged in the heart and brain of carnosine-treated aged rats (Figs. 2, 3).

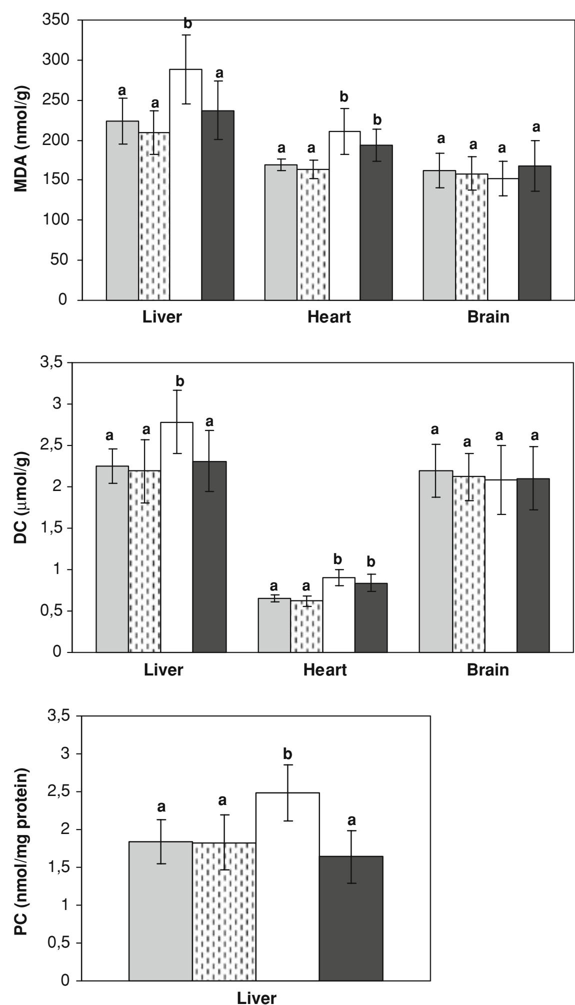

Fig. 1 Malondialdehyde (MDA) and diene conjugate (DC) levels in liver, heart and brain as well as protein carbonyl (PC) levels in liver of rats (Mean ± SD). Values not sharing a common letter are significantly different by Kruskal–Wallis test followed by Mann–Whitney U test; $P < 0.05$. untreated young rats ($n = 6$); carnosine-treated young rats ($n = 6$); untreated aged rats ($n = 8$); carnosine-treated aged rats ($n = 8$)

Discussion

Rat is one of the most suitable animals for studies of aging in mammals, since its life span is short and its nutrition can easily be controlled. Therefore, the relationship between oxidative stress and aging has been extensively examined in rats. In most of the studies male gender is especially preferred because females are known to be less susceptible to oxidative stress owing to estrogen's protection by decreasing

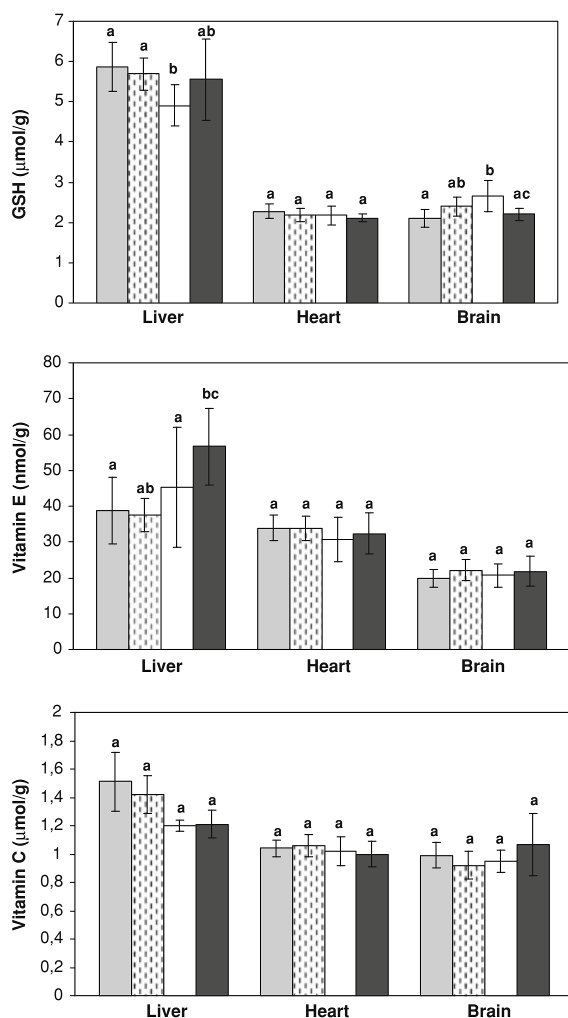

Fig. 2 Glutathione (GSH), vitamin E and vitamin C levels in liver, heart and brain of rats (Mean ± SD). Values not sharing a common letter are significantly different by Kruskal–Wallis test followed by Mann–Whitney U test; $P < 0.05$. ▭ untreated young rats ($n = 6$); ▭ carnosine-treated young rats ($n = 6$); ▭ untreated aged rats ($n = 8$); ▭ carnosine-treated aged rats ($n = 8$)

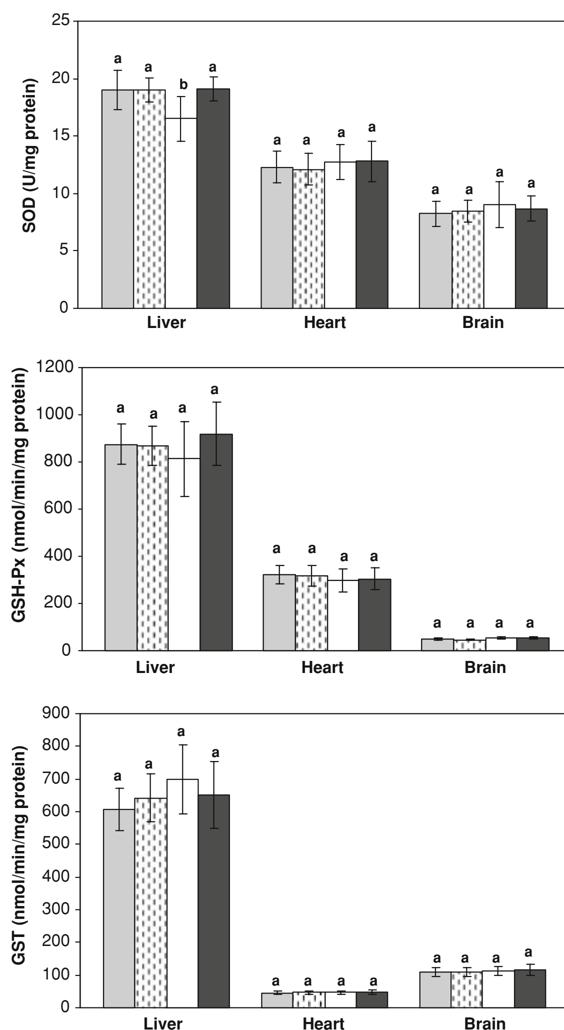

Fig. 3 Superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and glutathione transferase (GST) activities in liver, heart and brain of rats (Mean ± SD). Values not sharing a common letter are significantly different by Kruskal–Wallis test followed by Mann–Whitney U test; $P < 0.05$. ▭ untreated young rats ($n = 6$); ▭ carnosine-treated young rats ($n = 6$); ▭ untreated aged rats ($n = 8$); ▭ carnosine-treated aged rats ($n = 8$)

oxidative stress and increasing antioxidant defences (Vina et al. 2005).Oxidative stress parameters such as MDA levels (Tian et al. 1998; Siqueira et al. 2005; Jayakumar et al. 2007; Parıldar et al. 2008; Parıldar-Karpuzoğlu et al. 2008), protein carbonyls (Tian et al. 1998; Siqueira et al. 2005) and DNA damage (Wolf et al. 2005; Wong et al. 2006) have been investigated in young (4–6 months) and aged (20–24 months) male rats of different species. In these animals, non-enzymatic (Jayakumar et al. 2007; Parıldar et al. 2008; Parıldar-Karpuzoğlu et al. 2008) and enzymatic (Tian et al. 1998; Siqueira et al. 2005; Jayakumar et al. 2007; Parıldar et al. 2008; Parıldar-Karpuzoğlu et al. 2008) antioxidant systems are also determined. Although some data obtained from these studies happen to be controversial, a shift towards oxidant milieu in the cellular prooxidant–antioxidant balance is generally observed. The discripencies may be due to the difference in the susceptibility of organs and tissues to oxidative damage as well as the techniques

used for assessing oxidative stress in aged male rats. In the current study, liver MDA, DC and PC levels increased, while GSH and vitamin C levels and SOD activity decreased in aged rats. In the heart tissues, MDA and DC levels elevated without any changes in the antioxidant elements. On the other hand, no change was found in the prooxidant–antioxidant balance in the brain of aged rats. These results are in accordance with our previous studies (Parıldar et al. 2008; Parıldar-Karpuzoğlu et al. 2008).

Carnosine is proposed to have antioxidant activity which could attenuate the development of senile features (Boldyrev et al. 1999). Carnosine has been found to suppress senescence in cultured human fibroblasts and to protect telomeres of cultured cells against oxidative damage (Hipkiss 2005). Although its effect on lifespan of animals is known (Gallant et al. 2000; Yuneva et al. 2002), there is no study investigating the in vivo effect of carnosine on prooxidant–antioxidant balance in several tissues of aged animals. In the study of Ibrahim et al. (2008), carnosine was given to young rats alone or in combination with vitamin E as mixed in the diet. Carnosine supplementation up to levels of 1,000 mg/kg diet was not found to affect neither oxidation status nor antioxidant system of rat liver. In the current study, we investigated the in vivo effect of carnosine in liver, heart and brain tissues of young and aged rats. The data obtained about the effect of carnosine in young rats are similar to those of Ibrahim et al. (2008) despite the facts that mode of application and applied dose and application period were different. Although carnosine was not found effective in heart and brain tissues of aged rats; interestingly, in the liver tissue, it was efficient to lower the elevated MDA, DC and PC levels to those of control rats. This liver specific effect may be attributed to liver's rapidly taking up and using the absorbed carnosine. Indeed, supplemental carnosine has been found to significantly increase liver carnosine level when compared with extra-hepatic tissues as heart and muscle (Boissonneault et al. 1998). Carnosine is known to react with a variety of deleterious aldehydes to form carnosine-aldehyde adducts and to have a metal chelating effect (Aldini et al. 2005; Boldyrev 2005). Therefore, scavenging of free radicals, reacting with aldehydes, detoxifying aldehyde–modified proteins and chelating with redox metal ions may altogether contribute to the observed protective effect of carnosine in aged rats.

Vitamin E was also found significantly elevated in carnosine-treated aged rats. An in vivo interrelationship has been suggested to exist between vitamin E and carnosine (Maynard et al. 2001). Muscular vitamin E concentration was increased due to carnosine supplementation and interestingly, carnosine levels were found decreased due to vitamin E deficiency (Maynard et al. 2001). Our result supports this suggestion, and is consistent with that of our previous study of thioacetamide-induced liver injury (Mehmetçik et al. 2008).

Various conditions of oxidative stress are known to lead copper release from SOD molecule and result in enzyme molecule's fragmentation. Transition metals such as iron or copper react with hydrogen peroxide to produce hydroxyl radicals through Fenton-like reactions. In the current study, carnosine treatment is found to increase hepatic SOD activity in aged rats, which supports the fact that carnosine is a good scavenger of superoxide and hydroxyl radicals sparing SOD molecule (Kang et al. 2002). Beyond that, in copper-stimulated oxidations, its antioxidant action has also been attributed to its ability of chelating and inactivating copper. Therefore, carnosine is suggested to protect SOD from oxidative damage through the actions of copper chelating and radical scavenging (Kang et al. 2002). Indeed, Stvolinskii et al. (2003) have reported that in vivo carnosine treatment protected brain SOD under oxidative stress conditions such as hypobaric hypoxia and accelerated aging.

In conclusion, our results indicate that carnosine supplementation may have protective effects on age-dependent oxidative stress in liver tissue.

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